The prognostic role of Gustave Roussy Immune Score (GRIm-Score) in metastatic lung adenocarcinoma patients treated with chemotherapy

Gustave Roussy Immune Score (GRIm-Score) in metastatic lung adenocarcinoma

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Abstract

Aim: The Gustave Roussy Immune Score (GRIm-Score) in metastatic lung adenocarcinoma, based on the neutrophil-lymphocyte ratio, albumin and lactate dehydrogenase levels, divides patients into high and low-risk groups. In this study, we aimed to determine the prognostic role of GRIm-score in metastatic lung adenocarcinoma (LA) patients treated with chemotherapy.

Material and Methods: This was a retrospective, observational single-centre study. Patients who had metastatic LA (January 2018 – December 2018) were divided into two groups according to GRIm-score. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Cox regression analyses were performed to determine the risk factors independently associated with PFS and OS.

Results: Sixty patients [low-risk (n = 45), high-risk (n = 15)] were included in the study. The two groups had similar demographic characteristics and tumor features. In the low-risk and high-risk groups, the median PFS was 7.07 (95%CI: 5.79 – 8.34) and 4.53 (95%CI: 2.97 – 6.08) months (p = 0.009), respectively, and the median OS was 12.20 (95%CI: 8.70 – 15.69) and 7.70 (95%CI: 2.94 – 12.45) months (p = 0.03), respectively. The PFS and OS of the high-risk group were significantly worse than that of the low-risk group. Multivariate Cox regression analysis revealed that a high GRIM score was an independent risk factor for worse PFS (HR: 2.11; 95%CI: 1.13 – 3.95; p = 0.01) and OS (HR 1.87, 95% CI: 1.02 – 3.44, p = 0.04).

Discussion: GRIM score can be a guide in predicting the survival of metastatic LA patients treated with chemotherapy and can be used as a simple and easily accessible marker.

Keywords

Adenocarcinoma, Gustave-Roussy-Immune (GRIm)-Score, Lactate Hehydrogenase (LDH), Lung Cancer, Neutrophil-Lymphocyte Ratio (NLR)

Introduction

Non-small cell lung cancer (NSCLC) is one of the most frequent cancers and the leading cause of cancer-related deaths worldwide in recent years [1]. Lung adenocarcinoma is the most predominant subtype of NSCLC and its incidence is increasing. Most patients with lung adenocarcinoma are diagnosed in an advanced stage and the prognosis is poor [2]. Over the past decades, treatment options, including targeted therapy and immunotherapy, have ushered in a new era of anti-cancer treatment. Cytotoxic systemic chemotherapy also remains an important treatment for metastatic lung adenocarcinoma. Although major improvements have been made in lung cancer treatments, patient selection and assessment of the prognosis should be considered for more appropriate management strategies [3]. However, the identification of prognostic factors for poor outcomes among metastatic lung adenocarcinoma patients is still an important unmet need.

The Gustave Roussy Immune-score (GRIm-score) was first identified by Bigot et al in 2017 for better patient selection in phase I clinical trials for immunotherapies [4]. GRIM-score, based on the combination of neutrophil-to-lymphocyte ratio (NLR), serum albumin (Alb) and lactate dehydrogenase (LDH), all of which have been demonstrated to be potent prognostic markers reflecting host systemic immune-nutritional status, categorizes patients into different prognostic risk groups [5-7]. For NSCLC, several studies have reported that GRIm-score can be used as a prognostic marker for immunotherapy or surgery [5,7]. Moreover, the prognostic value of GRIm-Score also has been confirmed in various cancers [8,9]. However, as far as we know, little is known about whether the high GRIm-score is associated with poor outcomes in metastatic lung adenocarcinoma patients treated with chemotherapy. Therefore, the purpose of the current study was to evaluate the prognostic role of GRIm-score in metastatic lung adenocarcinoma patients treated with chemotherapy.

Material and Methods

Patients

We retrospectively investigated patients aged older than 18 years with metastatic lung adenocarcinoma who were treated with chemotherapy (± palliative radiotherapy if indicated) as first-line treatment according to the guidelines at our institution between January 2018 and December 2018 [10]. Patients were staged based on the 8th edition TNM staging system proposed by the International Association for the Study of Lung Cancer (IASLC) [11]. The exclusion criteria were: (1) a history of other malignant tumours; (2) recent clinical evidence of acute infection, inflammatory diseases, autoimmune diseases or trauma; (3) incomplete first-line anti-cancer therapy (due to death, low-performance status or self-refusal etc.) and (4) absence of clinical information (laboratory or radiological) or loss of follow-up (Figure 1).

Clinical characteristics included demographic data (age, sex, smoking comorbidity), tumor features (date of diagnosis, metastatic sites, number of metastatic sites, date of progression and death) and laboratory tests within 1 week of the initiation of anti-cancer treatment were recorded from our hospital's electronic medical record system or patients' files. GRIm-Score

was calculated based on NLR, serum lactate dehydrogenase and serum albumin for each patient as follows: Patients were assigned 1 point if they had NLR > 6, LDH > upper limit normal (Our hospital's upper limit of normal (ULN) LDH is 247 U/L) or albumin < 3.5 g/dL, for a total of 3 points. GRIm-Score 0-1 was considered low risk and 2-3 was considered high risk.

Primary survival outcomes were determined as progression-free survival (PFS) and overall survival (OS). PFS was considered as time (months) from the first treatment until radiological progression or death due to any cause /last follow-up (censored at last follow-up for patients alive and without progression), whichever occurred first [7]. OS was considered as the time (months) from the date of diagnosis of SCLC until the date of death from any cause or the last date of follow-up. Patients who were still alive and still did not show progression were censored at the final follow-up. The cut-off date for follow-up was March 1, 2023.

The study was approved by the ethics committee of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Decision no:2012-KAEK-15/2657 Date:22.02.2023) and performed in accordance with the Good Clinical Practice guidelines and assent specific to our country. The Declaration of Helsinki and its subsequent revisions were followed. As this study was retrospective, an informed consent form was waived.

Statistical Analysis

Categorical data were expressed as a number of cases (%) and compared using the Chi-square test or Fisher exact test. The normality of the distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Continuous data were given as mean ± standard deviation (SD) for normal distributions and were compared using Student's t-test for two independent groups. Continuous data were presented as medians and interquartile ranges (IQR) for skewed distributions and were compared using the Mann–Whitney test for two independent groups. The median follow-up duration was calculated using the reverse Kaplan-Meier method. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression model analysis was performed to identify risk factors independently associated with OS and PFS, and presented with the hazard ratios (HRs) and 95% confidence interval (95% CI). All significant variables, which were identified using the univariate Cox regression analysis ($p < 0.1$), were included in the multivariate Cox regression analysis. A p-value of < 0.05 was considered statistically significant. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. was used for statistical analyses.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Patient Characteristics

Sixty (11 (18.3%) females, 49 (81.7%) males, mean age 62.4 ± 8.6]) patients with metastatic lung adenocarcinoma were enrolled on the study. Most of the patients (n = 51, 85%) had a history of smoking and approximately half of the entire study population (n = 29, 48.3%) had at least one comorbidity.

Twenty-five (41.7%) patients had multiple metastatic sites (≥ 2 sides) and the most metastasis site was pleura/malign pleural effusion (n = 33, 55%), followed by bone (n = 21, 35%) and contralateral lungs (n = 15, 25%).

While 45 (75%) patients were in the low-risk group, 15 (25%) were in the high-risk group according to the GRIm-score. The demographic data (age, sex, smoking comorbidity) and tumour features (number and location of metastasis) were similar between the two groups. Regarding laboratory parameters, the high-risk group had significantly higher levels of neutrophil (6.2 (3.74) vs 5.2 (2.79), p = 0.02), LDH (274 (20.7) vs 207 (9.4), p = 0.001) and NLR (6.15 (0.68) vs 2.81 (0.24), p = 0.002) and lower levels of lymphocytes (1.44 ± 0.72 vs 1.92 ± 0.57, p = 0.01) and albumin (29.4 ± 0.43 vs 37.8 ± 0.48, p < 0.001) than those in the low-risk group. The remaining laboratory parameters (white blood cells, platelets, hemoglobin) were similar between the two groups (Table 1).

High GRIm-score was associated with worse PFS and OS

All patients, except one, progressed and died at the time of the last follow-up. The median PFS and OS of the entire population were 6.70 (95%CI: 5.86 - 7.53) and 10.03 (95%CI: 6.39 - 13.66) months, respectively. In the low-risk and high-risk groups, the median PFS was 7.07 (95%CI: 5.79 - 8.34) and 4.53 (95%CI: 2.97 – 6.08) months (p = 0.009), respectively (Figure 2a), and the median OS was 12.20 (95%CI: 8.70 - 15.69) and 7.70 (95%CI: 2.94 -12.45) months (p = 0.03), respectively (Figure 2b). The PFS and OS of the high-risk group were significantly worse than that of the low-risk group.

GRIm-score was an independent prognostic factor for PFS and OS

Univariate Cox regression analysis revealed that GRIm high-risk (HR: 2.25; 95%CI: 1.20 -4.19; p = 0.01) and presence of other metastases (HR: 0.53; 95%CI: 0.27 - 1.05; p = 0.007) were related to worse PFS. Multivariate Cox regression analysis indicated that only GRIm high risk (HR: 2.11; 95%CI: 1.13 -3.95; p = 0.01) was an independent risk factor for worse PFS (Table 2). Univariate Cox regression analysis also demonstrated that the presence of bone metastasis (HR: 1.64; 95%CI: 0.95 -2.83; p = 0.07) and GRIm high-risk (HR: 1.87; 95%CI: 1.02 - 3.42; p = 0.04) were associated with worse OS. GRIm high-risk (HR 1.87, 95% CI: 1.02- 3.44, p = 0.04) was only an independent prognostic factor for worse OS on multivariate Cox regression (Table 3).
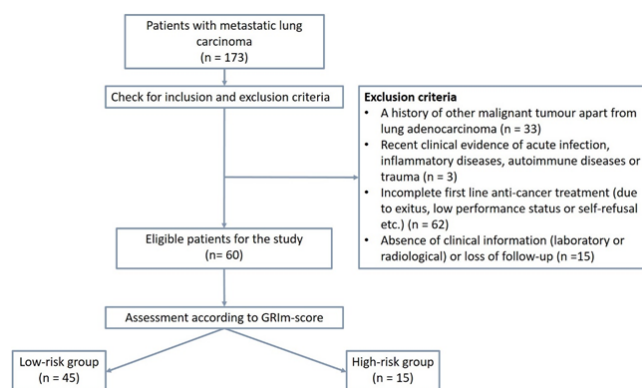
Figure 1. The flowchart of the study population. Abbreviations: GRIm-score, Gustave Roussy Immune (GRIm)-score.

Table 1. Baseline characteristics and laboratory parameters of the study population.
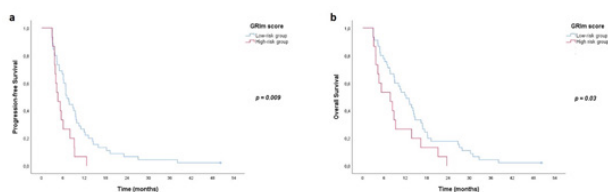
	All Population (n = 60)	Low-risk group (n = 45)	High-risk group (n = 15)	p-value
Age (year ± SD)	62.4 ± 8.6	62.7 ± 8.6	61.7 ± 8.9	0.7
Age, n (%)				
< 65 / ≥ 65	35 (58.3) / 25(41.7)	27 (60) / 18 (40)	8 (53.3) / 7 (46.7)	0.65
Sex, n (%)				
Female / Male	11 (18.3) / 49(81.7)	10 (22.2) / 35(77.8)	1 (6.7) / 14 (93.3)	0.26
Smoking (+), n (%)	51 (85)	39 (86.7)	12 (80)	0.53
Comorbidity (+), n (%)	29 (48.3)	22 (48.9)	7 (46.7)	0.88
Multiple metastasis (+) (≥ 2), n (%)	25 (41.7)	16 (35.6)	9 (60)	0.09
Metastasis sites, n (%)				
Contralateral Lung	15 (25)	10 (22.2)	5 (33.3)	0.49
Bone	21 (35)	13 (28.9)	8 (53.3)	0.08
Adrenal gland	11 (18.3)	9 (20)	2 (13.3)	0.71
Cranial	8 (13.3)	5 (11.1)	3 (20)	0.4
Pleura / MPE	33 (55)	22 (48.9)	11 (73.3)	0.09
Other	12 (20)	11 (24.4)	1 (6.7)	0.26
Laboratory parameters				
WBC (median, IQR)	8.27 (2.34)	8.14 (2.34)	8.88 (3.38)	0.18
Neutrophils (median, IQR)	5.6 (2.26)	5.2 (2.79)	6.2 (3.74)	0.02
Lymphocytes (mean ± SD)	1.8 ± 0.64	1.92 ± 0.57	1.44 ± 0.72	0.01
Platelets (median, IQR)	328 (16)	324 (15.6)	382 (23.2)	0.15
hemoglobin (mean ± SD)	12.8 ± 1.6	12.8 ± 1.6	12.6 ± 1.9	0.57
LDH (median, IQR)	218.5 (11.5)	207 (9.4)	274 (20.7)	0.001
albumin (mean ± SD)	35.7 ± 0.59	37.8 ± 0.48	29.4 ± 0.43	<0.001
NLR (median, IQR)	3.43 (0.27)	2.81 (0.24)	6.15 (0.68)	0.002

Abbreviations: WBC, white blood cell; IQR, interquartile range; SD, standard deviation; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; MPE, malignant pleural effusion

Table 2. Univariate and multivariate analyses of factors associated with progression-free survival.

Variables	Progression-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age						
< 65 (Ref)	1					
≥ 65	1.22	0.71 – 2.07	0.46			
Gender						
Female (Ref)	1					
Male	0.92	0.47 – 1.79	0.81			
Smoking						
No (Ref)	1					
Yes	0.83	0.40 – 1.71	0.61			
Comorbidities						
No (Ref)	1					
Yes	1.20	0.71 – 2.04	0.48			
Number of metastases						
< 2 (Ref)	1					
≥ 2	1.3	0.60 – 1.77	0.89			
Contralateral lung metastasis						
No (Ref)	1					
Yes	1.22	0.67 – 2.21	0.5			
Bone metastasis						
No (Ref)	1					
Yes	1.16	0.67 – 2.00	0.59			
Adrenal metastasis						
No (Ref)	1					
Yes	0.70	0.35 – 1.41	0.32			
Cranial metastasis						
No (Ref)	1					
Yes	1.70	0.79 – 3.65	0.16			
Pleural metastasis / MPE						
No (Ref)	1					
Yes	1.36	0.80 – 2.32	0.25			
Other metastases						
No (Ref)	1			1		
Yes	0.53	0.27 – 1.05	0.07	1.57	0.29 – 1.13	0.11
GRIm score						
Low-risk	1			1		
High-risk	2.25	1.20 – 4.19	0.01	2.11	1.13 – 3.95	0.01

Abbreviations: GRIm-score, Gustave Roussy Immune (GRIm)-score; MPE: Malignant pleural effusion

Table 3. Univariate and multivariate analyses of factors associated with overall survival.

Variables	Overall Survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age						
< 65 (Ref)	1					
≥ 65	1.43	0.84 – 2.42	0.18			
Gender						
Female (Ref)	1					
Male	0.75	0.38 – 1.46	0.4			
Smoking						
No (Ref)	1					
Yes	1.20	0.58 – 2.46	0.61			
Comorbidities						
No (Ref)	1					
Yes	1.18	0.70 – 1.98	0.51			
Number of metastases						
< 2 (Ref)	1					
≥ 2	1.5	0.61 – 1.80	0.85			
Contralateral lung metastasis						
No (Ref)	1					
Yes	1.24	0.69 – 2.25	0.46			
Bone metastasis						
No (Ref)	1			1		
Yes	1.64	0.95 – 2.83	0.07	1.64	0.94 – 2.86	0.07
Adrenal metastasis						
No (Ref)	1					
Yes	1.4	0.52 – 2.07	0.9			
Cranial metastasis						
No (Ref)	1					
Yes	1.48	0.69 – 3.17	0.3			
Pleural metastasis / malign effusion						
No (Ref)	1					
Yes	1.5	0.62 – 1.76	0.85			
Other metastases						
No (Ref)	1					
Yes	0.60	0.31 – 1.17	0.13			
GRIm score						
Low-risk	1			1		
High-risk	1.87	1.02 – 3.42	0.04	1.87	1.02 – 3.44	0.04

Abbreviations: GRIm-score, Gustave Roussy Immune (GRIm)-score; MPE: Malignant pleural effusion

Discussion

In the current study, we demonstrated the prognostic role of GRIm-score in metastatic lung adenocarcinoma. Our results revealed that GRIm-score independently predicts the prognosis and high GRIm-score is associated with poor outcomes in metastatic lung adenocarcinoma patients treated with chemotherapy.

Until today, it has been well established that biomarkers of systemic inflammation/nutritional status, including NLR, albumin and LDH, are associated with outcomes in NSCLC patients. Prior studies have concluded that systemic inflammatory response and nutritional status have a substantial impact on the occurrence, development, and metastasis of patients with lung cancer [12,13]. Gu et al. reported NLR to be potentially a useful

Figure 2. Kaplan-Meier plots of progression-free survival (a) and overall survival (b) according to the GRIm-score. Abbreviations: GRIm-score, Gustave Roussy Immune (GRIm)-score.

biomarker to predict the poor prognosis for NSCLC, suggesting that NLR could reflect the imbalance of pro- and anti-tumour activity of the hosts in respect of inflammatory response [14]. Similarly, NLR has also been found to be a prognostic maker in NSCLC patients treated with immunotherapy or NSCLC patients receiving adjuvant chemotherapy [15,16]. Serum albumin has also been proven to be closely associated with the advance and prognosis of cancer. As one of the negative acute phase reactants, albumin levels can reflect the inflammatory status. It can also present nutritional status, which can indicate disease severity, disease progression and prognosis [17,18]. In systemic reviews, low serum albumin level has been identified as a significant indicator of poor prognosis in patients with NSCLC [19,20]. LDH plays an important role in tumour metabolism through the regulation of anaerobic glycolysis, which is closely related to tumour cell proliferation. This enzyme also promotes tumour survival by inhibiting apoptosis and preventing necrosis in an anoxic environment [21]. Most studies have demonstrated that higher pretreatment LDH level was associated with worse OS in NSCLC patients [22-24].

Considering that the GRIm-score is a novel nutritional and inflammatory-based prognostic score and consists of NLR, albumin and LDH, it may also be a useful marker. GRIm-score using these parameters was first established by Bigot et al in ICT phase I trials population. They found that patients with a high GRIm-score had an inferior OS than patients with a low GRIm-score [4]. This score has also been studied in various cancers. For instance, the high GRIm-score group showed worse OS and disease-free survival compared with those in the low GRIm-score group in colorectal cancer patients and esophageal squamous cell carcinoma patients [9,25]. Furthermore, Lenci et al. reported no association between GRImT1 (GRIm-score at 45 days since treatment initiation), GRImΔ (GRIm-score difference between baseline and at 45 days since treatment initiation) and patient outcomes in advanced NSCLC patients treated with first-line chemotherapy, while a significant association was found in patients treated with pembrolizumab [7]. As far as we know, there was only one study that evaluated GRIm-score in lung adenocarcinoma patients treated with chemotherapy. This study conducted by Minami et al. demonstrated that the PFS and OS of low-score groups were significantly longer than those of high-score groups in wild-type EGFR adenocarcinoma [6]. Consistent with their results, the PFS and OS of the high-risk group were significantly worse than that of the low-risk group in our study. Furthermore, Minami et al. revealed that a high GRIm-score was an independent poor prognostic factor of OS of first-line cytotoxic chemotherapy [6]. Our study confirmed this result and also supported the usefulness of GRIm-score as a promising and useful pretreatment prognostic maker for this population.

Conclusion

The present study indicates that the GRIm score is an independent prognostic factor of poor outcomes for metastatic lung adenocarcinoma patients treated with chemotherapy. Additional prospective randomized clinical trials are required to comprehensively inquire into the prognostic role of the GRIm score.

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